

The Air Force Health Study An Overview and Update

17 June 2004



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The herbicide Agent Orange was a 1:1 mixture of 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and was contaminated, from less than 0.05 to almost 50 parts per million, with 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin). Dioxin is a toxic persistent organic pollutant not known to have been present in Agent Orange during the spraying. This contamination and subsequent concerns by veterans regarding exposure to Agent Orange and adverse health motivated many studies and reviews by the National Academy of Sciences.

A report by the National Academy of Sciences published in 2003 concluded that there is sufficient evidence of an association between exposure to herbicides and/or dioxin and chronic lymphocytic leukemia, soft-tissue sarcoma, Non-Hodgkin's lymphoma, Hodgkin's disease, and chloracne and limited/suggestive evidence of an association between dioxin or herbicide exposure and respiratory cancer, prostate cancer, multiple myeloma, acute and sub-acute transient peripheral neuropathy, porphyria cutanea tarda, Type 2 diabetes, and spina bifida in the children of Vietnam veterans.



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Herbicides were sprayed in Vietnam by the US Air Force Operation Ranch Hand between 1962 and 1971 using C-123 aircraft to defoliate in order prevent ambush and to reveal lines of communication. Army personnel also sprayed herbicides on the ground and from helicopters to defoliate the perimeters of base camps and fire bases for the same reason. From 1962 through 1965 small quantities of Agent Purple (2,4-D; 2,4,5-T), Blue (Cacodylic acid), Pink (2,4,5-T), and Green (2,4,5-T) were sprayed. From 1965 through 1970 more than 11 million gallons of Agent Orange (2,4-D; 2,4,5-T), as well as smaller quantities of White (2,4-D; picloram) and Blue were sprayed, and from 1970 through 1971 only Agents White and Blue were used for defoliation purposes. Only phenoxy herbicides, those containing 2,4,5-T, were contaminated with dioxin.



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Shown here is an area of Vietnam before spraying.



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A similar area after spraying is shown here.



Contents



- **Overview**
 - **Study design**
 - **Protocol issues**
 - **Reliability and validity of the dioxin measurement**
 - **Half life studies**
 - **Endpoints**
 - **Latest findings**

This overview will address all of these topics. Recent results in cancer, cognitive function, and peripheral neuropathy are included.



Goal



- **To conduct a 20-year prospective epidemiological study of herbicide exposure and health, mortality, and reproductive outcomes in veterans of Operation Ranch Hand**

The details of the Air Force Health Study design and subject selection are published. The study seeks to determine whether veterans of Operation Ranch Hand have experienced adverse health and whether those health effects, if any, can be attributed to exposure to herbicides or their dioxin contaminant. Ranch Hand veterans were exposed to herbicides during flight operations and maintenance of the aircraft and herbicide spray equipment. The study compares the health, mortality experience, and reproductive outcomes of Ranch Hand veterans with a comparison group of other Air Force veterans who served in SEA during the same period (1962 to 1971) that the Ranch Hand unit was active and who were not involved with spraying herbicides. Comparison veterans were matched to Ranch Hand veterans on date of birth, race (Black, non-Black) and military occupation (officer pilot, officer navigator, nonflying officer, enlisted flyer, enlisted ground crew).



- PROGRAM DIRECTION:
 - White House Domestic Affairs and Policy Ltr (16 Sep 80)
 - PMD 1092(10) /PE0605306F
 - Public Law 101-510, Sec. 1468 (5 Nov 90)
 - Public Law 102-4 (Agent Orange Act of 1991)

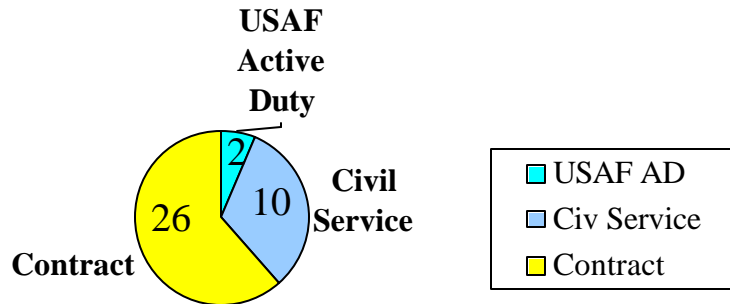
- POINTS OF CONTACT
 - IPT Leader: Mr Richard Ogershok, 311th HSW/YASP
 - Chief, Air Force Health Study Branch, Lt Col Julie Robinson, AFRL/HEDA
 - Primary User: Ranch Hand Advisory Committee (Dr L Schechtman, Executive Secretary)

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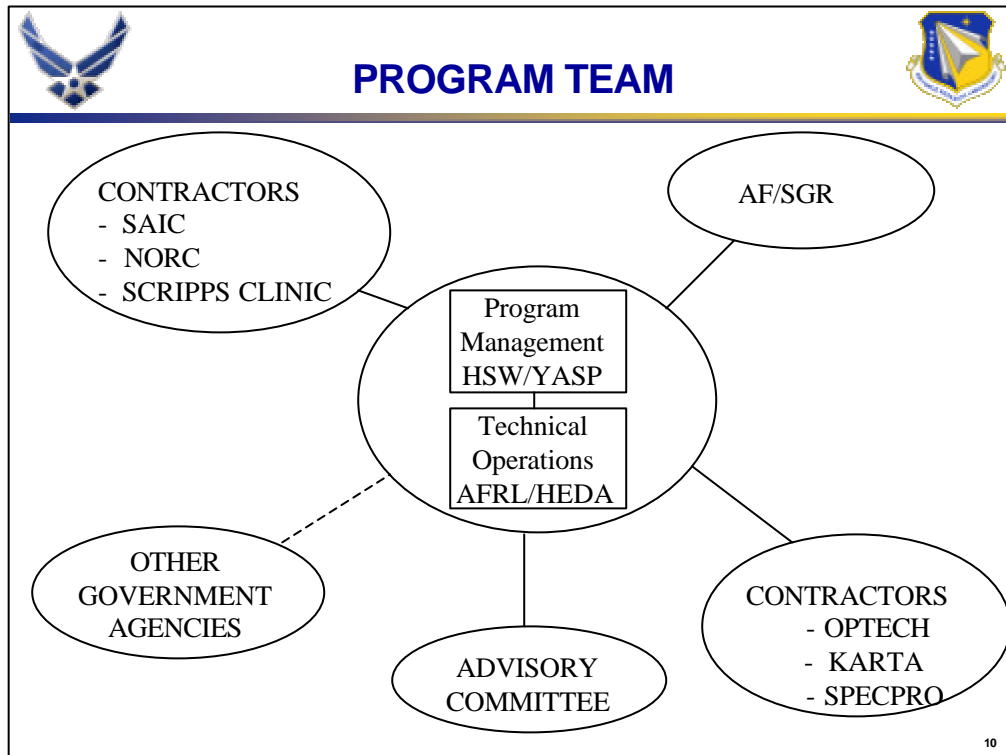
The study was launched by a letter from Mr Stuart Eisenstadt, Domestic Policy Counsel to the President, to the Secretary of Defense, in 1980. Subsequently, a program element was established and laws were passed to establish an advisory committee and task the National Academy of Sciences to periodically review Agent Orange scientific literature. The program is managed by Mr Richard Ogershok of the Human Systems Wing, and by Lt Col Julie Robinson, Chief of the Air Force Health Study Branch, Air Force Research Laboratory, Air Force Materiel Command. Our primary user is the USAF Surgeon General. The Ranch Hand Advisory Committee, administered by Dr Leonard Schechtman of the Food and Drug Administration, Department of Health and Human Services.



Staffing



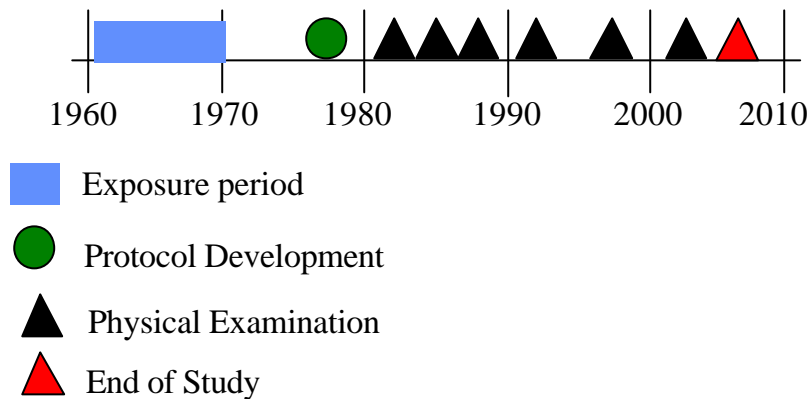
The study currently employs 2 active duty military, 10 civil servants and 26 contract personnel. Five of the 26 contractors work for the Air Force Mortality Registry, managed by the Air Force Institute for Operational Health.



Program management resides in HSW/YASP and technical management resides in AFRL/HEDA. Study staff interact with contract personnel at SAIC, NORC, and Scripps Clinic, who were responsible for conducting physical examinations, administering questionnaires, collecting and analyzing data, and writing reports. The Office of the Surgeon General (USAF/SGR) manages the program funding element. In-house contractors provide technical support (SpecPro) and program management support (Karta, OpTech). The Ranch Hand Advisory Committee reviews study results and methods every year. Study staff interact with other agencies, including CDC, NIEHS, NIH, and the DVA in special studies, exposure measurements, critical review of manuscripts, and interpretation of results.



Schedule



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This slide depicts the period of exposure, between 1962 and 1971, the protocol development between 1976 and 1978, and physical examinations in 1982, 1985, 1987, 1992, 1997, and 2002. The first examination was conducted at Kelsey Seybold Clinic in Houston, Texas, and all subsequent examinations were conducted by Scripps Clinic in La Jolla, California. Examination content was specified in the protocol, and was periodically reviewed by the Institutional Review Boards at the participating facilities. Participation was voluntary and informed consent was given at the examination sites. The study is scheduled to conclude on 30 September 2006.



Study Design



- **Index group: Ranch Hand veterans (N=1,209)**
- **Control population: Air Force veterans of Southeast Asia (N=19,078)**
- **Examined controls matched on age, race, military occupation (N=1,641)**

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Ranch Hand veterans (N=1,209) were exposed to herbicides during flight operations and maintenance of the aircraft and herbicide spray equipment. The entire population of Comparison veterans (N=19,078) is used in mortality studies. A subset of matched Comparisons was invited with the Ranch Hand veterans to participate in the periodic physical examinations (N=1,641). Non-compliant Comparisons were replaced by a health-matched Comparison in the same matched set following an algorithm prescribed in the protocol.



Study Design (Continued)



- **Exposure index: dioxin body burden**
- **Multiple endpoints**
- **Repeated physical examinations, interviews and mortality assessments**

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During protocol development, study investigators and reviewers recognized the limitations of existing records to provide an exposure index for each Ranch Hand veteran. Military spray records were used initially to compute an approximate index. In 1986, collaboration began with the Centers for Disease Control and Prevention to measure dioxin in serum. This measure was later incorporated into the study and served as a basis for several exposure indices. The study includes multiple endpoints and data is collected through repeated physical examinations, in-person interviews, and mortality assessments.



Morbidity Study Participation*



Year	Ranch Hand		Comparison	
	Eligible	Attended (%)	Eligible	Attended (%)
1982	1,209	1,046 (86.5)	1,666	1,223 (73.4)
1985	1,209	1,017 (84.1)	1,666	1,292 (77.6)
1987	1,199	996 (83.1)	1,713	1,298 (75.8)
1992	1,188	953 (80.2)	1,730	1,280 (74.0)
1997	1,149	870 (75.7)	1,761	1,251 (71.0)
2002	1,102	777 (70.5)	1,920	1,174 (61.1)

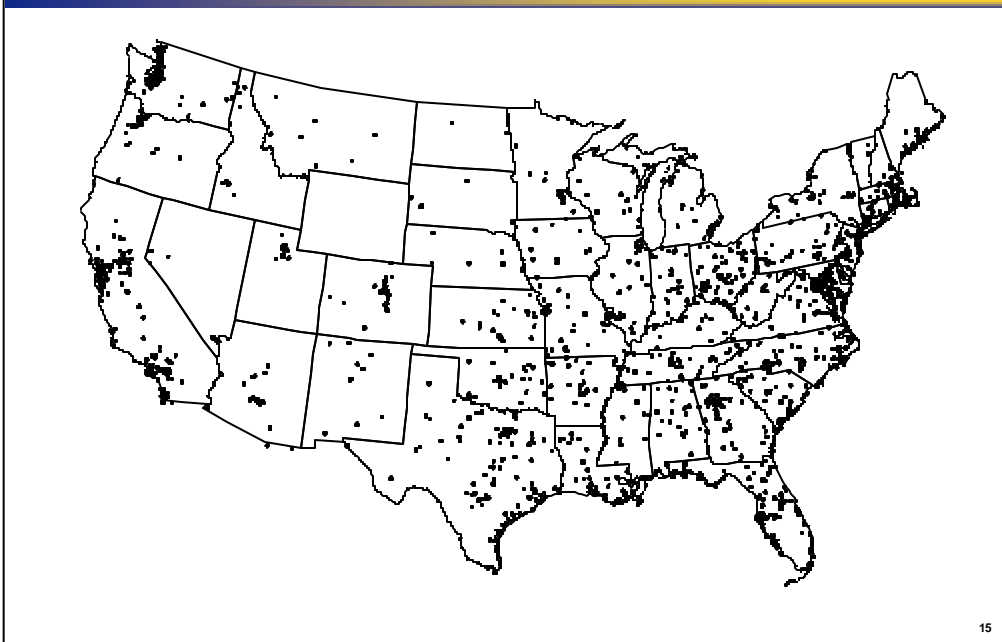
***Air Force Health Study 2002 Final Report (to be released at the end of 2005)**

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This slide summarizes study compliance from 1982 to 2002. During the study, Ranch Hand compliance dropped from 86.5% in 1982 to 70.5% in 2002 and Comparison compliance dropped from 73.4% in 1982 to 61.1% in 2002. All eligible veterans are invited to participate. Comparison compliance is maintained through replacement of non-compliant comparison veterans with a health-matched comparison from the same matched set, as specified in the protocol. Non-compliant Ranch Hand veterans cannot be replaced. Participation was voluntary and informed consent was provided at the examination sites.



Residential Locations



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In 1992, 2,180 of 2,233 participants (97.6%) lived in the 48 contiguous states, 26 (1.2%) lived in Hawaii, Alaska, Guam, or Puerto Rico, and 26 (1.2%) lived outside of the United States.



Protocol Issues (1977-1979)



- **Unprecedented scope**
- **Loss to follow-up, differential compliance**
- **Exposure assessment**
- **Credibility**

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The study protocol was reviewed by the Air Force Scientific Advisory Board, the Armed Forces Epidemiology Board, and the National Academy of Sciences. These issues were considered during the protocol writing period. The study was recognized as unusual due to its unprecedented scope. Study content was motivated by reported health conditions by Vietnam veterans at Veterans Administration hospitals, as recorded in the VA Herbicide Registry. Study investigators expected considerable loss to follow-up especially in the Comparison group and resultant differential compliance due to lack of interest by Comparisons. The lack of an accurate exposure index was recognized. Study investigators expected that study results might not be believed because the Air Force, rather than a non-governmental entity, would be conducting the study. To address that concern, an independently administered advisory committee of non-government scientists was established to oversee the study.



Design and Analysis Issues*



- **Exposure misclassification and bias (1979)**
- **Measurement error in half-life studies (1992)**
- **Validity of the dioxin body burden (1995)**
- **Reliability of the dioxin assay (1996)**
- **Bias in the half-life studies (1999)**

*Each issue was studied and the results were published
In the year given in parentheses.

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The limitations of the spray records to provide an accurate exposure index were recognized in 1979; **misclassification and bias** calculations related to the index were included in the protocol. In April 1987 the dioxin assay was introduced in a study of 200 Ranch Hand and 50 Comparison veterans who had blood drawn at one of four Red Cross Clinics in Los Angeles, Tulsa, Cleveland, and Atlanta. The assay introduced a new set of issues, including measurement error, validity, reliability, and bias in half-life studies. Measurements of dioxin were made by CDC and the first results were published in the MMWR in 1988. The effect of **measurement error in the assay on the estimation of half-life** was analytically derived and published in 1992. The results showed that the error in the estimated decay rate is relatively small when the time interval between measurements is within 60% of the half-life, as is the case in the Air Force Health Study. A questionnaire administered to Ranch Hand enlisted personnel to elicit information regarding skin exposure provided a basis for **validity** studies, published in 1995. The results showed a correlation between reported skin exposure and dioxin body burden. Paired dioxin measurements on 47 veterans who gave blood at the Red Cross Clinics and at the 1987 physical examination provided a basis for **reliability** studies, published in 1996. The dioxin assay exhibited very high reliability in log units across the entire range of values and in original units up to 50 parts per trillion. Repeated dioxin measurements in 343 Ranch Hand veterans with dioxin levels greater than 10 parts per trillion in 1987 provided a basis for half-life studies of dioxin in these men. The method of selection was known to **bias estimates of the elimination rate**. Theoretical work began in 1992 and an algorithm to provide unbiased estimates was published in 1999.



Exposure Indices



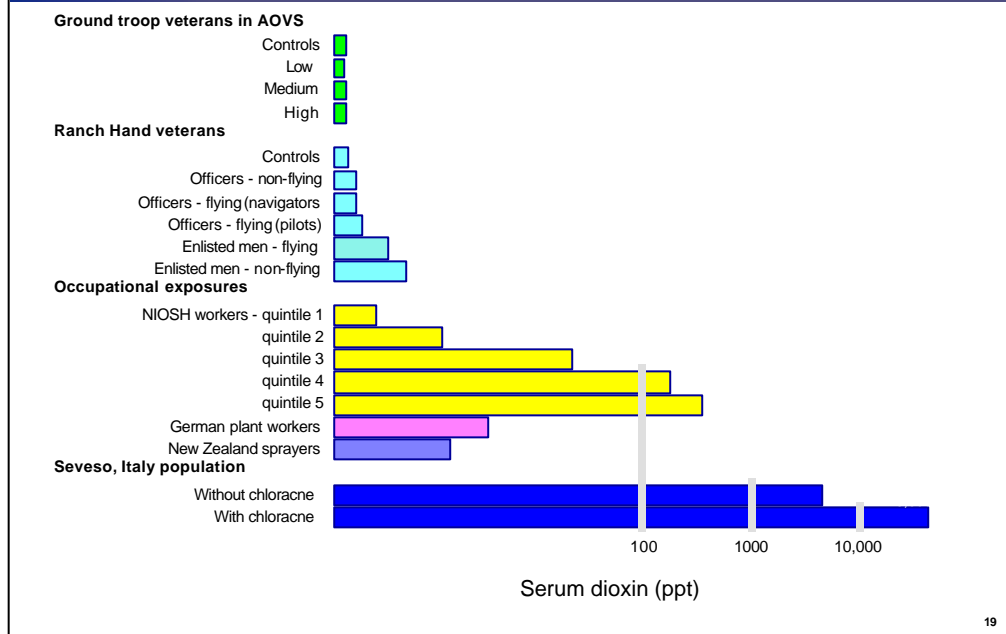
Year	Index
1978 (Protocol)	Flights ´ Gallons ´ Days ´ Concentration
1982, 1985, 1987	Gallons ´ Concentration/persons
1987, 1992, 1997, 2002	Dioxin body burden

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This slide outlines attempts to define an exposure index. During protocol development, we multiplied flights by gallons sprayed, by days on the job by dioxin concentration to produce a metric. The required data were soon found lacking and so this method was dropped and replaced by a simpler formula involving only gallons sprayed, dioxin concentration, and the number of men on the job. During and after the 1987 examination, the dioxin assay, the estimated initial dose, group, and military occupation were used as exposure indices. More recently, we have used the cumulative dose derived from a first order pharmacokinetic model.



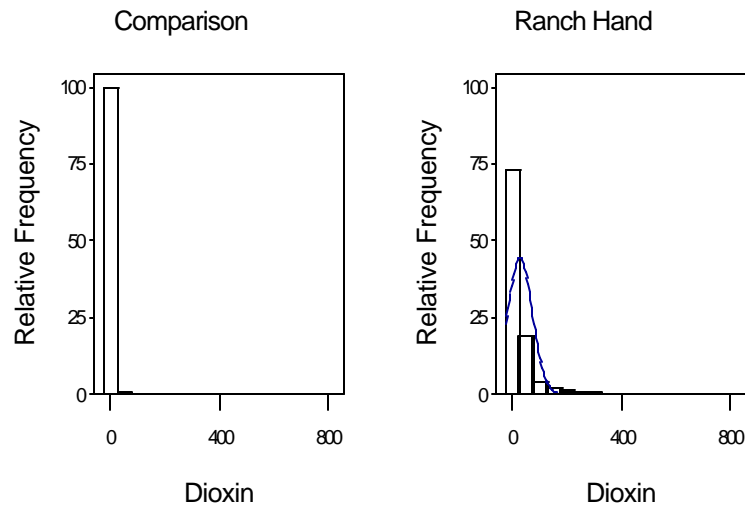
Median dioxin levels in selected populations



This slide depicts the relative position of Air Force Health Study dioxin levels compared to the Army ground troop study, the NIOSH studies of industrial workers who made Agent Orange and other herbicides, German chemical factory workers, New Zealand herbicide sprayers, and studies of victims of a chemical plant explosion in Seveso, Italy, in 1976. The Ranch Hand initial dose, about 4000 ppt is about 10% of the maximum dose received by victims of the Seveso accident. The bars give the mean dioxin level in 1987 in study participants. The Seveso bars give dioxin levels measured within 3 years after the accident. Members of the CDC Agent Orange Vietnam Study had background levels similar to Air Force Health Study Comparison veterans.



Dioxin (ppt) by Group

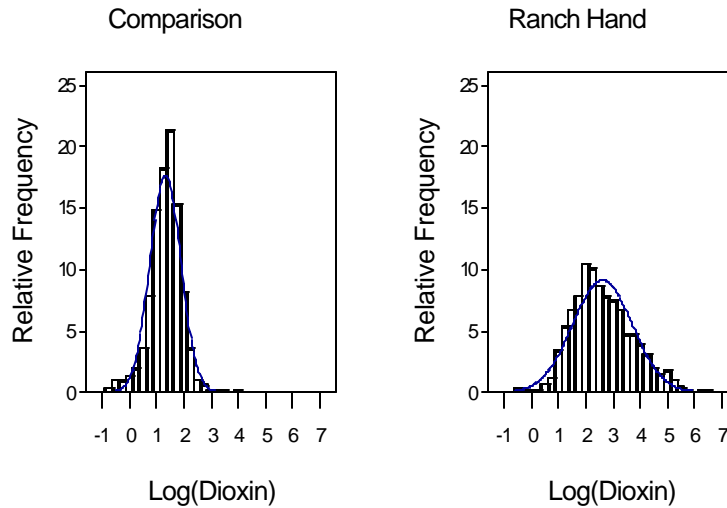


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Histograms of dioxin in Comparison and Ranch Hand veterans measured in 1987 and subsequently are shown. 98% of Comparison dioxin values were less than 10 parts per trillion (ppt); the highest Comparison dioxin level was 54.8 ppt. The median Ranch Hand dioxin level was 12 ppt and the maximum was 617 ppt.



Log(Dioxin) by Group



These dioxin data are approximately log-normally distributed, evidenced by the near-bell shape after log transformation. The log-normality of the dioxin measurement simplified the statistical analyses of health and dioxin and facilitated the analysis of repeated dioxin measures in our pharmacokinetic studies.



Reliability of the Dioxin Measurement



- **47 Ranch Hands with paired measurements, April 1987 (at Red Cross clinics), and at the 1987 physical examination**
- **Coefficient of reliability (R) and confidence interval (CI)**
 - **On log scale: $R=0.96$, 95% CI 0.93-0.98**
 - **Original units up to 50 ppt: $R=0.87$, 95% CI 0.76-0.94**

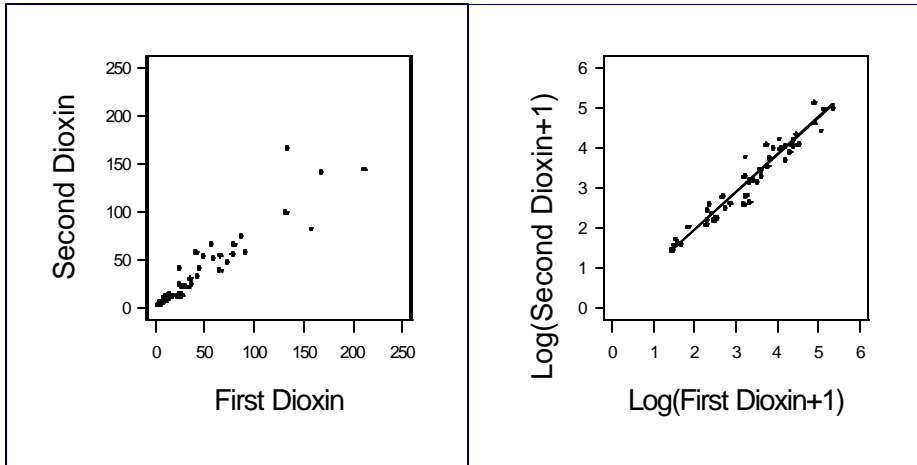
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A reliability study was conducted based on paired dioxin results from 47 Ranch Hand veterans who gave blood for the dioxin assay at Red Cross Clinics and at the 1987 physical examination.

The coefficient of reliability was 0.96 in log units and 0.87 in original units up to 50 parts per trillion (ppt). This means that 96% of the variation in dioxin measurements between individuals is caused by true individual differences and 4% is caused by measurement error.



Paired Dioxin Results (N=47)



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These scatter plots and overlaid best-fit least-square lines show these paired data in original and log units. The tight scatter in log units reflects the high reliability of the dioxin measurement on the log scale.



Validity of the Dioxin Measurement



- **Questionnaire mailed to all enlisted Ranch Hands (1989)**
- **Queried**
 - **entering the spray tank**
 - **using herbicide as a hand cleaner**
 - **servicing spray nozzles**
 - **wearing herbicide soaked clothing**
 - **operating spray system in flight**

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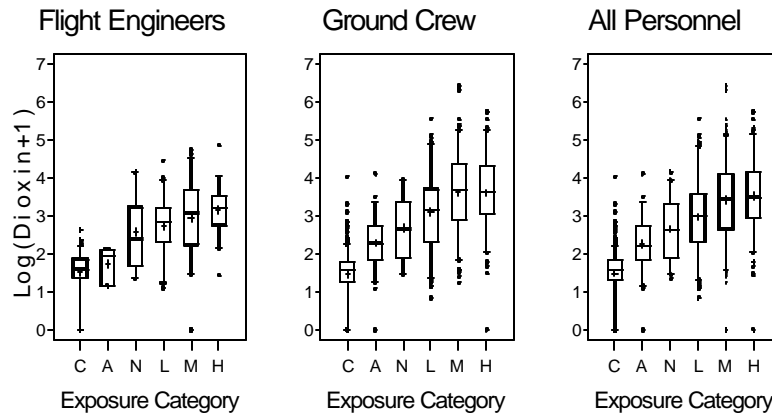
To assess the validity of the dioxin assay we developed a questionnaire and mailed it to Ranch Hand enlisted personnel. The purpose of the questionnaire was to investigate the association between reported herbicide exposure and serum dioxin concentration. We wrote the questionnaire by interviewing two Ranch Hand ground crew veterans regarding their work-related experiences and by studying maintenance manuals for the equipment used. We administered the questionnaire in 1989, prior to the veterans learning their individual dioxin body burdens.

The questionnaire addressed specific duties performed before, during, and after the spray missions; it elicited multiple-choice, fill-in-the-blank and narrative responses and accommodated a range of exposures, from none to extreme. We considered five routes of exposure: (1) entering the spray tank to service the dump valve, (2) using herbicide as a hand cleaner, (3) servicing the spray nozzles, (4) wearing clothing soaked with herbicide and (5) experiencing exposure while operating the spray system during flight.

The (1000 gallon) spray tank had an emergency "dump" valve in the bottom, designed for rapid dumping of the herbicide. This valve needed periodic lubrication requiring entry through a hatch in the top of the tank. The tank was never completely empty of herbicide. The herbicide easily removed grease from skin and these men had no reservations about using it as a hand cleaner.



Dioxin and Skin Exposure Category

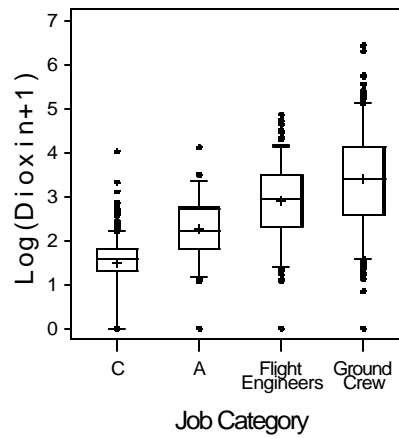


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Shown are graphs of dioxin in log units versus skin exposure category. A skin exposure index was defined as the number of days of skin exposure. Ranch Hand veterans were categorized to Administrators (A), those who reported no exposure (N), and among those who reported skin exposure, to tertiles of the index, named Low, Medium and High. A significant positive relation between skin exposure category and dioxin level in log units was found in flight engineers, ground crew, and all enlisted personnel.



Dioxin and Job Category



C=Comparison, A=Administrator

A strong positive relation between dioxin levels and job category was found, as shown.



Pharmacokinetic Studies



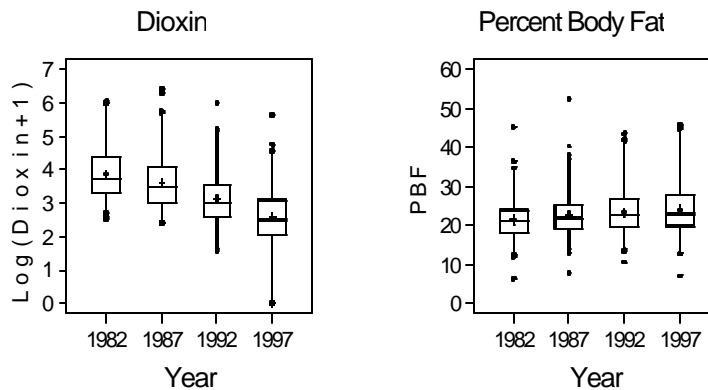
- **Ranch Hands included if 1987 dioxin >10 ppt**
- **Least squares estimate is biased due to inclusion criterion**
- **Iterative bias correction published in 1999**
- **Latest half-life study published in 1999**
 - **Half life=7.6 years**
 - **95% CI 7.0-8.2 years**

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A pharmacokinetic study of dioxin elimination was conducted. A veteran was included in the pharmacokinetic study if a) his dioxin measurement in 1987 was greater than 10 parts per trillion (ppt), a value regarded as a threshold for background exposure, b) he had provided serum in 1982 and c) the dioxin measurement in the serum collected in 1982 was quantifiable. A total of 343 veterans were included and 278 also received a quantifiable third dioxin measurement in 1992. In 1997, a fourth serum dioxin assay was offered to veterans included in the pharmacokinetic study. Participation was voluntary and consent forms were signed at the examination site. Two hundred ninety-one of the 343 veterans attended the 1997 physical examination and 283 had a quantifiable dioxin result. Sixty of the 343 veterans did not receive a dioxin result in 1997 because they either (1) died prior to the 1997 physical examination [n=8], (2) did not attend the 1992 physical examination [n=44], (3) attended the examination but were too ill to donate a blood sample [n=4], (4) attended the examination but did not donate blood [n=2], or (5) attended and donated blood but one or more of the multiple quality control checks were not within acceptable limits and insufficient sample was available for a repeat analysis [n=2]. An iterative bias correction was published in 1999, which gave the latest half-life estimate, 7.6 years with 95% confidence interval 7 to 8.2 years.



Dioxin and Percent Body Fat by Year

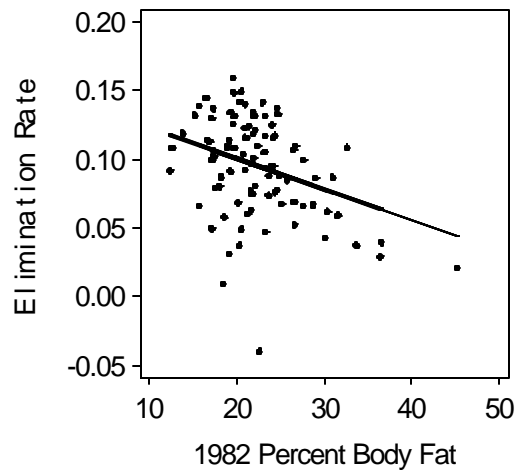


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This slide shows the decreasing dioxin distributions and the increasing body fat in the veterans included in the pharmacokinetic studies. The rate of decrease of dioxin was estimated and used to estimate the initial dose received in Vietnam. Percent body fat is an important determinant of the decay rate and has been used as a covariate in analyses of health and dioxin body burden.



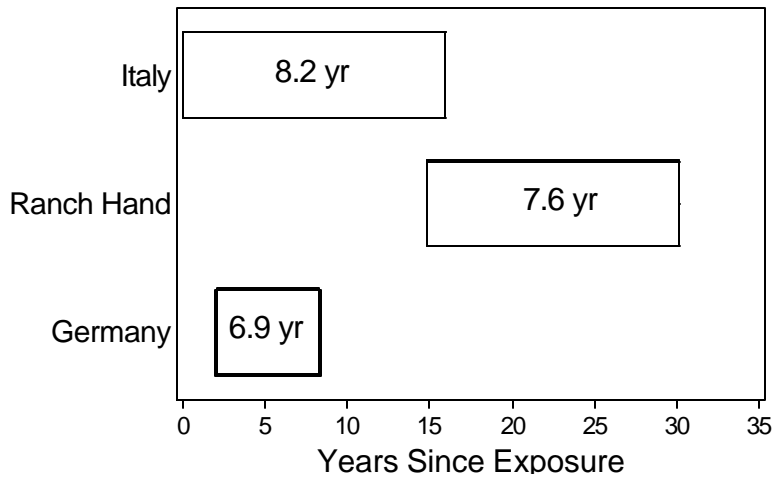
Elimination Rate and 1982 Percent Body Fat



The elimination rate was found to decrease significantly with increased body fat, as shown here. Heavier individuals have a smaller elimination rate and longer half life than thin individuals. This dependence of the elimination rate and half life on percent body fat has been observed in other studies and is the basis for our statistical adjustment for percent body fat in analyses of health outcomes.



Three Half-Life Estimates



Seveso: Needham et al 1994, Germany: Flesch-Janys et al 1994

The Ranch Hand half-life estimate is of the same order of magnitude as those provided by a study of victims of the chemical factory explosion in Seveso, Italy, and in a study of chemical factory workers in Germany.



Morbidity Endpoints



- General Health
- Cancer
- Neurological
- Psychological
- Gastrointestinal
- Dermatological
- Endocrinological
- Immunological
- Pulmonary
- Cardiovascular
- Renal

Over two hundred measures of health are included in the study, derived from a review of dioxin toxicology studies and data provided by 46,771 Vietnam veterans participating in the VA Herbicide Registry prior to 1979. These measures were grouped into the areas specified and were analyzed in our periodic reports and published articles.



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Medical coders use the rules and conventions of the International Classification of Diseases to code health records and death certificates for the underlying cause of death. Coders also provide quality control checks of data and records.



A Brief Summary of the Latest Findings

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Some of the latest findings are discussed. Several thousand statistical analyses of health outcomes and measures have been conducted, summarized in 10,000 pages of periodic reports and 50 published articles. This summary is selective, emphasizing health outcomes of statistical significance and those that have been mentioned by the National Academy of Sciences in their periodic reviews of the scientific literature.



Analysis Methods



- **Group contrasts**
 - **All Ranch Hand vs all Comparison**
 - Officer**
 - Enlisted Flyer**
 - Enlisted Ground**
- **Extrapolated initial dioxin level**
- **Dioxin exposure category**
- **Dioxin level**

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Four approaches are used to assess health versus exposure to herbicides. **First**, all Ranch Hands are contrasted with all Comparisons, and by occupational stratum. This analysis depends on an assumption that all Ranch Hand veterans were exposed and Comparison veterans were not exposed to herbicides.

Second, among Ranch Hand veterans, health is regressed on the estimated initial dioxin level, extrapolated to the time of tour using a first order model.

Third, Ranch Hand veterans in Background, Low and High dioxin exposure categories (defined on the next slide) are contrasted with Comparison veterans.

Fourth, health is regressed on dioxin measured in 1987.



Dioxin Exposure Category



Category	Definition*	Frequency
Comparison	Comparison	1,394
RH Background	RH, $D \leq 10$	442
RH Low	RH, $D > 10$, $I \leq 117.6$	281
RH High	RH, $D > 10$, $I > 117.6$	286

*D=dioxin, I=initial dioxin

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Four dioxin exposure categories, defined here, have been used since 1991. Ranch Hand veterans with dioxin level of no more than 10 parts per trillion (ppt) were assigned to the Background category; those above 10 ppt are assigned to the Low or High category depending on their extrapolated initial dioxin level in Vietnam. The value 117.6 is the median initial dioxin level among those with greater than 10 ppt.



Power: Ranch Hand High vs Comparison



Outcome	RR	Power (%)
Skin cancer	2.0	100
Any cancer	1.5	87
Abnormal skin test of cell-mediated immunity	2.5	83
Low sperm count	15.0	92
Spontaneous abortion	2.0	100
Any birth defect	2.0	100

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Study power is limited by the sample sizes. The power of this study is good for common conditions, such as skin cancer, any cancer, abnormal skin test of cell-mediated immunity, spontaneous abortion, and any birth defect, and poor for rare conditions, such as low sperm count. Power is the likelihood that a study will detect an association specified by a relative risk. Birth defects and the occurrence of spontaneous abortion were determined from medical records reproductive outcomes after service in Southeast Asia.



Dioxin Category and Demographics



Ranch Hand

	C	Bkg	Low	High
Mean Birth Year	1938	1937	1937	1941
Mean Tour Year	1968	1968	1968	1968
Officer (%)	37	60	38	3
Enlisted (%)	63	40	62	97

C=Comparison

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There is variation in birth year and military occupation by dioxin category. Ninety-seven percent of veterans in the High category were enlisted and most in the Background category were officers. This difference explains the birth year difference between these two categories because (not shown on this slide) officers were, on the average, 5 years older than enlisted personnel. The mean tour year was 1968 in all four dioxin categories; overall, 50% of the tours were between 1967 and 1970 (not shown on the slide).



Morbidity Results



Endpoint	Findings
General Health	+
Cancer	+
Neurology	+
Psychology	+
Gastrointestinal	±
Cardiovascular	±

+: significant adverse finding

±: significant adverse findings and non-significant findings

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The next two slides summarize very briefly thousands of statistical analyses. To see these, visit our web page and download our reports. Self-perception of health, one of three subjective measures studied in general health, was significantly and adversely associated with dioxin exposure category in 1992 and 1997, with Ranch Hands in the high dioxin exposure category reporting a worse self-perception than Comparisons. Analyses of cancer on the entire cohort published in 1999 did not find an association with dioxin exposure. However, an analysis published in 2004 showed a significant increase in the risk of melanoma in Ranch Hand veterans and a significant increase of the risk of prostate cancer in both cohorts versus national rates. When restricted to Ranch Hands who spent most or all of their Southeast Asia tour of duty in Vietnam and to Comparisons who spent little or none of their Southeast Asia tour of duty in Vietnam, the risk of all-site cancer, prostate cancer, and melanoma was increased with dioxin level in the Ranch Hand group. We found an increased risk of probable peripheral neuropathy in Ranch Hand veterans in the High dioxin exposure category. Analyses of psychological abnormalities as measured by the MMPI found no associations with herbicide or dioxin exposure, however, an analysis of the Wechsler Memory Scale found an increased mean reduction in immediate and delayed recall in the High dioxin exposure category. An analysis of hepatic function found increases in the mean of a liver enzyme (GGT) in the High dioxin exposure category but no increase in liver disease. Analyses of cardiovascular disease found an increased risk of death from heart disease in Ranch Hand enlisted ground crew, but no corresponding adverse associations with dioxin among those who attended physical examinations.



Morbidity Results



Endpoint	Findings
Hematology	±
Endocrinology	+
Immunology	-
Pulmonary	±
Dermatology	-
Renal	-

+: significant adverse finding

±: significant adverse findings and non-significant findings

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In relation to hematological function, we studied red blood cell count, hemoglobin, hematocrit, mean corpuscular volume, white blood cell count, platelet count, and erythrocyte sedimentation rate. Mean corpuscular volume and platelet count generally increased with dioxin in Ranch Hand veterans. The increases in these measures among the highly exposed were modest and were considered unlikely to be of clinical significance. With regard to the endocrine system, we studied diabetes, gonadotropins, and sperm abnormalities. Glucose abnormalities, diabetes prevalence, and the use of oral medications to control diabetes increased, while time to diabetes onset decreased with dioxin in Ranch Hand veterans. Serum insulin abnormalities increased with dioxin in non-diabetics. Testosterone, follicle stimulating hormone, or leuteinizing hormone abnormalities were not related with dioxin, however, the testosterone mean decreased with dioxin. We found no relation between sperm count or the percentage of abnormal sperm and dioxin. Regarding the immune system, we studied delayed-type hypersensitivity skin test responses to *Candida albicans*, mumps, *Trichophyton*, and staphage lysate. Lymphocyte measurements included total lymphocyte counts, T (CD3, CD4, CD5, CD8), B (CD20), and NK (CD16 and CD56) subsets, and expression of the activation antigen CD25 on CD3 T cells. We quantitated the serum concentrations of IgG, IgA, and IgM, examined sera for the presence of monoclonal immunoglobulins, and looked for a broad range of autoantibodies. We found no evidence of a consistent relation between dioxin exposure category and immune system alteration. None of the Ranch Hand veterans was diagnosed as having chloracne, and found no meaningful or consistent association between dioxin exposure and acne.



All-site Cancer to July 1997



Ranch Hand				
	Comparison (N=1,200)	Bkg (N=375)	Low (N=228)	High (N=241)
N (%)	226 (18.8)	76 (20.3)	68 (29.8)	41 (17.0)
RR		1.1	1.8	0.9
95% CI		0.8-1.5	1.3-2.5	0.6-1.3

RR=relative risk, CI=confidence interval

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The next eight slides summarize cancer results to July 1997 on the entire cohort. There was an increased risk of cancer in the Low but not the High dioxin exposure category, a pattern difficult to interpret and not consistent with the expected dose-response.



Basal Cell Carcinoma to July 1997



	Comparison (N=1,133)	Ranch Hand		
		Bkg (N=359)	Low (N=210)	High (N=229)
N (%)	150 (13.2)	56 (15.6)	42 (20.0)	23 (10.0)
RR		1.2	1.6	1.0
95% CI		0.8-1.7	1.1-2.4	0.6-1.6

A pattern similar to that of all-site cancer was found for basal cell carcinoma.



Melanoma to July 1997



		Ranch Hand		
	Comparison	Bkg	Low*	High*
	(N=1,133)	(N=359)	(N=210)	(N=229)
N (%)	12 (1.1)	7 (2.0)	5 (2.4)	4 (1.8)
RR		1.6	2.2	2.7
95% CI		0.6-4.2	0.7-6.5	0.8-9.7

* Low and High combined versus Comparisons: p=0.06

The risk of melanoma was increased in the High exposure category, but the increase was not significant.



Systemic Cancer to July 1997



		Ranch Hand		
	Comparison	Bkg	Low	High
	(N=1,211)	(N=378)	(N=234)	(N=242)
N (%)	73 (6.0)	21 (5.6)	34 (14.5)	11 (4.6)
RR		0.7	1.9	0.9
95% CI		0.4-1.3	1.2-3.2	0.4-1.8

The risk of systemic cancer was increased in the Low but not in the High dioxin exposure category.



Liver Cancer to July 1997



Ranch Hand				
	Comparison (N=1,211)	Bkg (N=378)	Low (N=234)	High (N=242)
N (%)	2 (0.2)	0 (0.0)	0 (0.0)	2 (0.8)
RR				5.7
95% CI				0.8-41.5

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Based on two cases, there was a non-significant increase in the risk of liver cancer in the High dioxin exposure category.



Kidney and Bladder Cancer to July 1997



Ranch Hand				
	Comparison (N=1,211)	Bkg (N=378)	Low (N=234)	High (N=242)
N (%)	6 (0.5)	4 (1.1)	5 (2.1)	2 (0.8)
RR		2.3	4.4*	3.3
95% CI		0.5-10.4	1.0-19.0	0.5-23.2

*P=0.04

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The risk of cancer of the kidney and bladder was increased in the Low dioxin exposure category. Based on 2 cases, the risk was non-significantly increased in the High category.



Prostate Cancer to July 1997



	Comparison (N=1,211)	Ranch Hand		
		Bkg (N=378)	Low (N=234)	High (N=242)
N (%)	39 (3.2)	9 (2.4)	12 (5.1)	4 (1.7)
RR		0.5	0.9	0.6
95% CI		0.2-1.1	0.4-2.0	0.2-1.9

*P=0.04

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The risk of prostate cancer was not increased in any of the Ranch Hand dioxin exposure categories. Other analyses adjusted for years served in Southeast Asia (shown later in this presentation) found an adverse association between prostate cancer and dioxin exposure category.



Counts of Rare Cancers to July 1997



Ranch Hand				
	Comparison (N=1,211)	Bkg (N=378)	Low (N=234)	High (N=242)
STS*	2	0	0	1
Hodgkins	3	1	0	0
NHL*	3	1	0	0
Lymphoid Histiocytic	2	2	0	0
*STS: soft tissue sarcoma, NHL: non-Hodgkin Lymphoma				

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Specific cancers such as these were too few to analyze.



Heart Disease to July 1998



		Ranch Hand		
	Comparison	Bkg	Low	High
	(N=1,195)	(N=376)	(N=233)	(N=243)
N (%)	730 (61.1)	259 (68.9)	163 (70.0)	139 (57.2)
RR		1.3	1.3	1.0
95% CI		1.0-1.8	1.0-1.8	0.8-1.4

48

An analysis of heart disease found an increased risk in the Low but not in the High dioxin exposure category.



Diabetes to June 1995



		Ranch Hand		
	Comparison (N=1,276)	Bkg (N=422)	Low (N=284)	High (N=283)
N (%)	169 (13.2)	40 (9.5)	49 (17.2)	57 (20.1)
RR		0.7	1.3	1.5
95% CI		0.5-1.0	1.0-1.7	1.2-2.0

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In an analysis published in *Epidemiology* in 1997, the risk of diabetes increased with dioxin exposure category. The risk in the High category was significantly increased. These data, together with those of other studies, contributed to a conclusion by the Institute of Medicine, National Academy of Sciences, that the evidence relating diabetes and dioxin was suggestive, but that the role of chance or bias could not be ruled out.



Diabetes to July 1998



		Ranch Hand		
	Comparison	Bkg	Low	High
	(N=1,183)	(N=375)	(N=232)	(N=238)
N (%)	199 (16.7)	37 (9.8)	49 (20.9)	57 (23.8)
RR		0.7	1.2	1.5
95% CI		0.5-1.0	0.8-1.8	1.0-2.2

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The corresponding diabetes data from the 1997 physical examination showed a similar pattern to that of the previous slide.



Thyroid Stimulating Hormone 1987



		Ranch Hand		
Comparison		Bkg	Low	High
(N=1,247)		(N=409)	(N=273)	(N=275)
Mean	0.83	0.84	0.87	0.90
P-value		0.88	0.16	0.04

Test for trend: $p=0.003$

The mean thyroid stimulating hormone was significantly increased in the High dioxin exposure category in 1987. These data were subsequently published in 2003. The full analysis found no significant relation between the occurrence of thyroid disease and dioxin category. The findings suggested that dioxin affects thyroid hormone metabolism and function in Ranch Hand veterans.



Peripheral Neuropathy



- **Included veterans compliant to at least one of the first 5 examinations**
- **Standard neurological examination**
- **Nerve conduction velocity in 1982**
- **Vibrotactile measurement in 1997**

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In an article published in 2001, we studied peripheral neuropathy and dioxin exposure category using information from a standard neurological examination, nerve conduction velocities, and vibrotactile measurements.



Probable Peripheral Neuropathy



- **Defined as the presence of at least two bilateral abnormalities:**
 - **Achilles reflex**
 - **Ankle vibration**
 - **Pin prick (foot)**

We defined probable peripheral neuropathy as the occurrence of at least two bilateral abnormalities of the Achilles reflex, ankle vibration, or pin prick on the feet.



Probable Peripheral Neuropathy*



	Comparison (N=1,086)	Ranch Hand		
		Bkg (N=338)	Low (N=213)	High (N=210)
N (%)	22 (2.0)	8 (2.4)	8 (3.8)	14 (6.7)
RR*		1.5	1.4	5.0
95% CI		0.6-3.5	0.6-3.4	2.2-11.2

*Determined at the 5th physical examination in 1997 and 1998.

The risk of probable peripheral neuropathy was significantly increase in the High dioxin exposure category.



Cognitive Functioning



- **Included veterans compliant to the baseline (1982) examination**
- **Cognitive tests administered at baseline**
 - **Halstead-Reitan neuropsychological test battery**
 - **Wechsler Adult Intelligence Scale-revised**
 - **Wechsler Memory Scale**
 - **Reading subtest of the Wide Range Achievement Test**

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We administered the Halstead-Reitan (HR) Neuropsychological Test Battery, the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Wechsler Memory Scale (WMS) Form I, and the reading subtest of the Wide Range Achievement Test (WRAT) at the baseline physical examination in 1982 to assess cognitive functioning in Ranch Hand veterans. We studied cognitive functioning and dioxin exposure category and summarized the results in an article published in 2001. The HR test battery included the following subtests and outcome measures: (1) the Category Test, an assessment of problem solving ability, judgment, abstract reasoning, and concept formation, (2) the Tactual Performance Test, an assessment of tactile perception and memory, and visuospatial performance, (3) the Seashore Rhythm Test – an assessment of auditory rhythmic pattern discrimination, attention, concentration, and coordination among ear, eyes, and hand, (4) the Speech-Sounds Perception Test, an assessment of auditory verbal discrimination, attention, and concentration, (5) the Finger-Tapping Test, an assessment of motor speed and coordination, (6) Grip Strength, an assessment of motor strength using a hand dynamometer, (7) Trail-Making Tests A and B, an assessment of attention, perceptual ability, problem solving, motor speed, and coordination. For the WAIS-R, we examined age-adjusted scores on the information, digit span, vocabulary, arithmetic, comprehension, similarities, picture completion, picture arrangement, block design, object assembly, and digit symbol subscales, verbal IQ, performance IQ, and full-scale IQ. For the WMS, we analyzed logical memory (immediate and delayed), visual reproduction, and associate learning subtests. For the WRAT, we examined the raw reading score.



Logical Memory, Immediate Recall



	Comparison (N=1,052)	Ranch Hand		
		Bkg (N=388)	Low (N=274)	High (N=275)
Mean	7.5	7.3	7.2	7.0
Difference		-0.2	-0.2	-0.50
95% CI		-0.5, 0.2	-0.6, 0.2	-0.9, -0.1

Mean logical memory scores on the WMS were significantly decreased in the Ranch Hand High exposure category.



Logical Memory, Immediate Recall Enlisted Veterans



	Comparison (N=659)	Ranch Hand with herbicide skin contact (N=460)
Mean	6.7	6.2
Difference		-0.5
95% CI		-0.9, -0.2
P-value		<0.001

The logical memory decrement became sharper when we contrasted enlisted Ranch Hand veterans who experienced skin exposure to herbicides with enlisted Comparison veterans.



Cancer to 31 December 1999

**A recent analysis published in 2004,
adjusting for tour date, time in Vietnam,
and military occupation**

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Following a recommendation from the Ranch Hand Advisory Committee, we re-analyzed cancer incidence and mortality (through 31 December 1999), with adjustment for tour date, time spent in Vietnam, and military occupation.



Analysis Plan



- **Observed and expected cancer incidence referenced to US males**
- **Observed and expected cancer mortality referenced to US males**
- **Cancer prevalence and dioxin category adjusted for time spent in Vietnam**

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We contrasted observed and expected cancer incidence and mortality in both cohorts (Ranch Hand, Comparison) relative to the national rates for US males. We conducted internal analyses of cancer prevalence based on dioxin exposure category, contrasting Ranch Hands in the High, Low and Background categories with Comparison veterans. All analyses were adjusted for time spent in Vietnam.



Cancer Incidence and Mortality



- **Period at risk: from end of service in Southeast Asia to 31 December 1999***
- **All outcomes confirmed by record review**
- **ICD rules**
- **SEER categories**

*Previously reported to 10 July 1997

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Incident cases from the end of service in Southeast Asia to 31 December 1999 were verified by review of medical records and death certificates. Coding of records followed the rules and conventions of the International Classification of Diseases. Cancers were grouped into categories defined by the Surveillance Epidemiology and End Results (SEER) section of the National Cancer Institute. Previous analyses included cases verified to have occurred after service in Southeast Asia to 10 July 1997 (summarized in previously in this presentation).



Exposure Period Category



- **Stratified by tour date category**
 - **1961 (no spraying)**
 - **1962 to 1965 (pre-Agent Orange)**
 - **1966 to 1970 (predominantly Agent Orange)**
 - **1971 to 1972 (post-Agent Orange)**
 - **1973 to 1975 (no spraying)**

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To account for variation across time in the types and quantities of herbicides sprayed by Operation Ranch Hand, we assigned each veteran to one of four tour date categories defined by the year his tour ended; these were 'Before 1962 or After 1972' (when no herbicide was sprayed), '1962-1965' (pre-Agent Orange), '1966-1970' (predominantly Agent Orange) and '1971-1972' (Post Agent Orange). Spraying of Agent Orange was suspended on 15 April 1970.



Occupation Category



- **Officer (pilots, navigators, administrators)**
- **Enlisted flyers**
- **Enlisted ground crew**

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We assigned each veteran to one of three military occupation categories (officer, enlisted flyer, enlisted ground). Ranch Hand enlisted ground crew have the highest dioxin levels, followed by enlisted flyers. Officers have the lowest levels.



Exposure Opportunity Categories



- **At most 2 years in Southeast Asia (SEA)**
 - **Ranch Hand: majority of SEA time in Vietnam**
 - **Comparison: majority of SEA time outside of Vietnam**
- **Vietnam experience**
 - **Ranch Hand: 100% of SEA tour in Vietnam**
 - **Comparison: 0% of SEA tour in Vietnam**

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We attempted to isolate a “Vietnam” effect two ways: by a) restricting time spent in SEA to at most 2 years, and b) by restricting Comparison veterans to those who spent 0% and Ranch Hand veterans to those who spent 100% of their SEA service in Vietnam. The 2-year cut point was chosen after an examination of scatter plots of the percentage of SEA service spent in Vietnam versus years spent in SEA in an attempt to identify Ranch Hand veterans who spent the majority of their SEA service in Vietnam and Comparison veterans who spent the majority of their SEA service outside of Vietnam. The 2-year cut point appeared to provide the best single cut to serve this purpose. To this end, we assigned each veteran to one of two categories of time spent in SEA, defined by ‘At most 2 years in SEA’, and ‘More than 2 years in SEA’. We also assigned each veteran to one of two categories of the percentage of SEA service spent in Vietnam, defined by ‘Comparison: 0% and Ranch Hand: 100%’ and ‘Comparison: >0% and Ranch Hand: <100%’.



Analysis



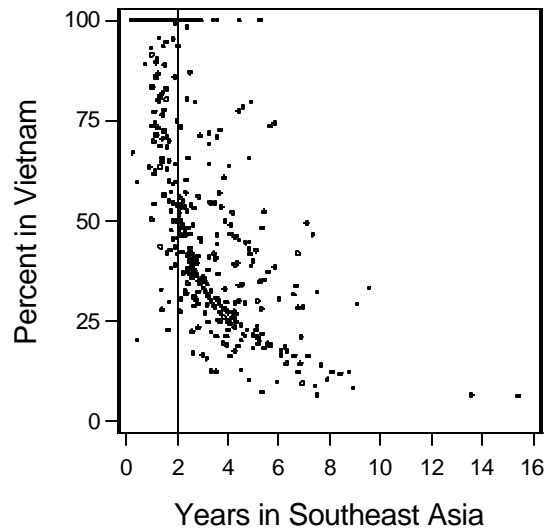
- **External contrasts**
 - **Cancer incidence and mortality versus SEER rates for US males, adjusted for age, race, calendar period**
 - **Stratified by tour date, occupation, exposure opportunity category**
- **Internal contrasts**
 - **Cancer prevalence by dioxin category**
 - **Stratified by exposure opportunity category**

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We conducted external contrasts, comparing observed with expected cancer incidence and mortality referenced to national rates for US males, stratified by tour date, occupation, and exposure opportunity category. We also conducted internal analyses of cancer prevalence, comparing each of the three Ranch Hand dioxin exposure categories with Comparisons, stratified by exposure opportunity category.



Ranch Hand Percent of tour spent in Vietnam by Years in Southeast Asia

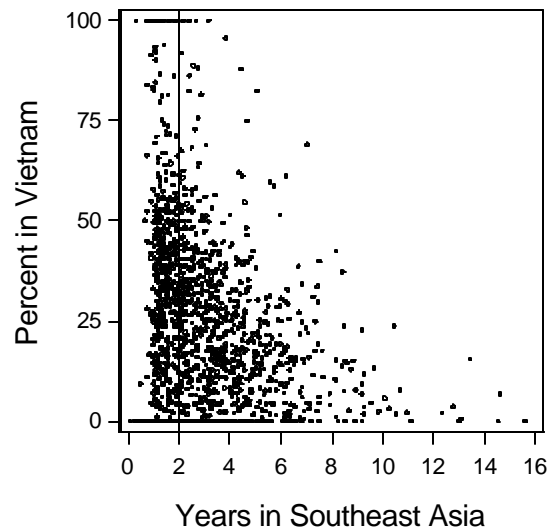


65

This slide shows that the 2 year cut on time spent in Southeast Asia tends to select Ranch Hand veterans who spent the majority of their Southeast Asia tour of duty in Vietnam.



Comparison Percent of Tour Spent in Vietnam by Years in Southeast Asia



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This slide shows that the 2 year cut on time spent in Southeast Asia tends to select Comparison veterans who spent the majority of their Southeast Asia tour of duty outside of Vietnam.



Sample Reduction



Status	Ranch Hand	Comparison	Total
At least one exam	1,196	1,785	2,981
Cancer pre-SEA	7	9	16
External Net	1,189	1,776	2,965
Missing dioxin	180	347	527
Internal Net	1,009	1,429	2,438

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The study includes veterans who were partially or fully compliant to at least one of 5 physical examinations in 1982, 1985, 1987, 1992 or 1997 (n=2,981). Veterans with cancer prior to their service in Southeast Asia were excluded from all analyses. Those with missing dioxin values were excluded from the internal contrasts.



Dioxin Exposure Category



Category	Definition	Frequency ¹
Comparison	Comparison	1,246
RH Background	RH, $D^2 \leq 10$	404
RH Low	RH, $D > 10$, $I^3 \leq 118.5$	247
RH High	RH, $D > 10$, $I > 118.5$	247

1: White, 2: D=dioxin, 3: I=initial dioxin

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Sample sizes by dioxin exposure category are shown for White veterans. The median initial dioxin level among Ranch Hand veteran with dioxin values greater than 10 ppt was 118.5 ppt. We restricted to White Ranch Hand veterans to remain consistent with our external contrasts against national rates that were based on incidence rates for US White males.



At most 2 years in Southeast Asia



Category	Definition*	Frequency ¹
Comparison	Comparison	580
RH Background	RH, $D^2 \leq 10$	287
RH Low	RH, $D > 10$, $I^3 \leq 118.5$	151
RH High	RH, $D > 10$, $I > 118.5$	174

1: White, 2: D=dioxin, 3: I=initial dioxin

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The corresponding sample sizes in veterans who spent at most 2 years in Southeast Asia are shown. The Comparison sample size was reduced more than the Ranch Hand sample sizes, reflecting different tour patterns in the two cohorts.



Percent of tour spent in Vietnam Ranch Hand 100% Comparison 0%



Category	Definition*	Frequency ¹
Comparison	Comparison	291
RH Background	RH, D ² ≤10	252
RH Low	RH, D>10, I ³ ≤118.5	132
RH High	RH, D>10, I>118.5	165

***1: White, 2: D=dioxin, 3: I=initial dioxin**

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The sample sizes in Ranch Hand veterans who spent 100% of their Southeast Asia tour in Vietnam and Comparison veterans who spent 0% of their Southeast Asia tour in Vietnam are shown.



Ranch Hand Person-Years by Tour Date Category



Stratum	White	Black	Other
All	29,724	1,995	1,655
Before 1962 or after 1972	0	0	0
1962-1965	3,468	169	176
1966-1970	25,323	1,825	1,451
1971-1972	933	0	28

Ranch Hand person-years by tour date category are shown. Most tours occurred between 1966 and 1970, the period of heaviest Agent Orange spraying.



Comparison Person-Years by Tour Date Category



Stratum	White	Black	Other
All	42,578	2,986	2,913
Before 1962 or after 1972	516	0	0
1962-1965	2,827	265	283
1966-1970	33,297	2,405	2,107
1971-1972	5,937	316	522

Comparison person-years are shown by tour date category. Similar to Ranch Hand veterans, most tours occurred between 1966 and 1970.



Ranch Hand Cancer Incidence¹



Site	OBS ²	EXP ³	SIR ⁴	P-value
Any SEER site	134	123	1.09	0.34
Digestive	16	26	0.61	0.03
Respiratory	33	29	1.13	0.47
Lung & Bronchus	30	25	1.20	0.33
Melanoma	17	7	2.33	<0.001
Genitalia	38	27	1.42	0.04
Prostate	36	25	1.46	0.03

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

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Among White Ranch Hands, the incidence of melanoma, cancer of the genitalia, and prostate cancer was significantly increased and the incidence of cancer of the digestive system was significantly decreased relative to national rates, adjusted for year of birth and calendar period.



Comparison Cancer Incidence¹



Site	OBS ²	EXP ³	SIR ⁴	P-value
Any SEER site	163	173	0.94	0.47
Digestive	31	36	0.85	0.38
Respiratory	48	40	1.20	0.22
Lung & Bronchus	45	34	1.31	0.08
Melanoma	15	10	1.46	0.15
Genitalia	55	36	1.51	<0.001
Prostate	54	33	1.62	<0.001

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

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Comparison incidence of cancer of the genitalia and prostate was significantly increased relative to national rates.



Ranch Hand Prostate Cancer Incidence by Occupation¹



Occupation	OBS ²	EXP ³	SIR ⁴	P-value
Officer	17	14	1.24	0.38
Enlisted Flyer	9	4	2.05	0.05
Enlisted Ground	10	7	1.52	0.20

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

Among Ranch Hand veterans, the risk of prostate cancer was significantly increased among enlisted flyers.



Ranch Hand Melanoma Incidence by Occupation¹



Occupation	OBS ²	EXP ³	SIR ⁴	P-value
Officer	10	3	3.02	<0.001
Enlisted Flyer	0	1	0.00	
Enlisted Ground	7	3	2.62	0.03

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

Among Ranch Hand veterans, the risk of melanoma was significantly increased in officers and enlisted ground personnel.



Comparison Prostate Cancer Incidence by Occupation¹



Occupation	OBS ²	EXP ³	SIR ⁴	P-value
Officer	30	18	1.68	0.01
Enlisted Flyer	11	5	2.05	0.03
Enlisted Ground	13	10	1.28	0.37

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

Among Comparison veterans, the risk of prostate cancer was significantly increased in officers and enlisted flyers.



Comparison Melanoma Incidence by Occupation¹



Occupation	OBS ²	EXP ³	SIR ⁴	P-value
Officer	9	5	1.93	0.07
Enlisted Flyer	2	2	1.20	0.73
Enlisted Ground	4	4	1.02	0.91

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

Among Comparison veterans, the risk of melanoma was not significantly increased in any occupational category.



Ranch Hand Prostate Cancer Incidence by Year of Tour¹



Year of tour	OBS ²	EXP ³	SIR ⁴	P-value
Before 1962 or after 1972	0	0		
1962-1965	2	4	0.53	0.38
1966-1970	34	20	1.68	0.005
1971-1972	0	1	0	

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

Among Ranch Hand veterans the risk of prostate cancer was significantly increased in those whose tour of duty occurred between 1966 and 1970.



Ranch Hand Melanoma Incidence by Year of Tour¹



Year of tour	OBS ²	EXP ³	SIR ⁴	P-value
Before 1962 or after 1972	0	0		
1962-1965	1	1	1.16	
1966-1970	16	6	2.57	<0.001
1971-1972	0	0	0	

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

Among Ranch Hand veterans the risk of melanoma was significantly increased in those whose tour of duty occurred between 1966 and 1970.



Comparison Prostate Cancer Incidence by Year of Tour¹



Year of tour	OBS ²	EXP ³	SIR ⁴	P-value
Before 1962 or after 1972	1	0.5	2.17	
1962-1965	7	4	1.96	0.10
1966-1970	42	25	1.64	0.003
1971-1972	4	4	1.06	0.85

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

Among Comparison veterans the risk of prostate cancer was significantly increased in those whose tour of duty occurred between 1966 and 1970.



Comparison Melanoma Incidence by Year of Tour¹



Year of tour	OBS ²	EXP ³	SIR ⁴	P-value
Before 1962 or after 1972	0	0	0.00	
1962-1965	1	1	1.29	
1966-1970	12	8	1.51	0.17
1971-1972	2	1	1.47	0.55

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

Among Comparison veterans, the risk of melanoma was not significantly increased in any tour date category.



Ranch Hand Prostate Cancer Incidence by Exposure Opportunity Category¹



Category	OBS ²	EXP ³	SIR ⁴	P-value
At most 2 years in SEA	21	14	1.54	0.06
100% of SEA in Vietnam	17	10	1.66	0.05

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

Among Ranch Hand veterans, the risk of prostate cancer was significantly increased among those who spent 100% of their Southeast Asia tour of duty in Vietnam.



Ranch Hand Melanoma Incidence by Exposure Opportunity Category¹



Category	OBS ²	EXP ³	SIR ⁴	P-value
At most 2 years in SEA	11	5	2.36	0.01
100% of SEA in Vietnam	12	4	3.05	<0.001

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

Among Ranch Hand veterans, the risk of melanoma was significantly increased among those who spent at most 2 years in Southeast Asia and among those who spent 100% of their Southeast Asia tour of duty in Vietnam.



Comparison Prostate Cancer Incidence by Exposure Opportunity Category¹



Category	OBS ²	EXP ³	SIR ⁴	P-value
At most 2 years in SEA	7	10	0.68	0.31
0% of SEA in Vietnam	3	5	0.59	0.37

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

Among Comparison veterans, the risk of prostate cancer was not significantly increased in those who spent at most 2 years in Southeast Asia or in those who spent 0% of their Southeast Asia tour of duty in Vietnam.



Comparison Melanoma Incidence by Exposure Opportunity Category¹



Category	OBS ²	EXP ³	SIR ⁴	P-value
At most 2 years in SEA	3	4	0.72	0.62
0% of SEA in Vietnam	2	2	0.98	0.94

1: White, 2: Observed, 3: Expected, 4: Standardized Incidence Ratio

Among Comparison veterans, the risk of melanoma was not significantly increased in those who spent at most 2 years in Southeast Asia or in those who spent 0% of their Southeast Asia tour of duty in Vietnam.



Ranch Hand Cancer Mortality¹



Site	OBS ²	EXP ³	SMR ⁴	P-value
Any site	45	62	0.73	0.03
Digestive	6	14	0.42	0.02
Respiratory	21	24	0.87	0.54
Prostate	2	3	0.70	0.69
Genitalia	0	0.3	0.00	
Urinary System	1	1	0.89	
CNS	3	2	1.33	0.58

1: White, 2: Observed, 3: Expected, 4: Standardized Mortality Ratio

Ranch Hand mortality from cancer was not significantly increased relative to national rates.



Comparison Cancer Mortality¹



Site	OBS ²	EXP ³	SMR ⁴	P-value
Any site	67	86	0.78	0.03
Digestive	14	20	0.70	0.17
Respiratory	38	34	1.13	0.44
Prostate	3	4	0.77	0.70
Genitalia	0	0.4	0	
Urinary System	1	1.57	0.64	
CNS	1	3	0.31	

1: White, 2: Observed, 3: Expected, 4: Standardized Mortality Ratio

Comparison cancer mortality was not significantly increased relative to national rates.



Cancer at Any SEER Site, at most 2 years in Southeast Asia¹



	Comparison (N=580)	Ranch Hand		
		Bkg (N=287)	Low (N=151)	High (N=174)
N (%)	34 (5.9)	28 (9.8)	22 (14.6)	15 (8.6)
RR²		1.4	2.2	2.0
95% CI		0.8, 2.5	1.2, 4.0	1.0, 4.0

1: White, 2: Relative risk, 3: Confidence Interval

Among White veterans who spent at most 2 years in Southeast Asia, Ranch Hand veterans in the Low and High dioxin exposure categories have experienced a significantly increased risk of cancer at any site.



Cancer at Any SEER Site, Ranch Hand 100% Comparison 0%¹



	Comparison (N=291)	Ranch Hand		
		Bkg (N=252)	Low (N=132)	High (N=165)
N (%)	17 (5.8)	25 (9.9)	19 (14.4)	12 (7.3)
RR ²		2.6	3.8	3.3
95% CI ²		1.0, 6.8	1.5, 9.7	1.3, 8.9

1: White, 2: Relative risk, 3: Confidence Interval

Among White Ranch Hand veterans who spent 100% of their Southeast Asia tour of duty in Vietnam, those in the Low and High dioxin exposure categories have experienced significantly increased risk of cancer at any site.



Prostate Cancer at most 2 years in Southeast Asia¹



	Comparison (N=580)	Ranch Hand		
		Bkg (N=287)	Low (N=151)	High (N=174)
N (%)	7 (1.2)	10 (3.5)	6 (4.0)	5 (2.9)
RR ²		1.5	2.2	6.0
95% CI ³		0.5, 4.4	0.7, 6.9	1.5, 24.6

1: White, 2: Relative risk, 3: Confidence Interval

Among White veterans who spent at most 2 years in Southeast Asia, Ranch Hand veterans in the High dioxin exposure category have experienced a significantly increased risk of prostate cancer.



Melanoma at most 2 years in Southeast Asia¹



Ranch Hand				
	Comparison (N=580)	Bkg (N=287)	Low (N=151)	High (N=174)
N (%)	3 (0.5)	4 (1.4)	4 (2.7)	3 (1.7)
RR ²		3.0	7.4	7.5
95% CI ³		0.5, 16.8	1.3, 41.0	1.1, 50.2

1: White, 2: Relative risk, 3: Confidence Interval

Among White veterans who spent at most 2 years in Southeast Asia, Ranch Hand veterans in the Low and High dioxin exposure categories have experienced a significantly increased risk of melanoma.



Prostate Cancer Ranch Hand 100% Comparison 0%



	Comparison (N=580)	Ranch Hand		
		Bkg (N=287)	Low (N=151)	High (N=174)
N (%)	3 (1.0)	9 (3.6)	4 (3.0)	4 (2.4)
RR		2.5	2.4	4.7
95% CI		0.4, 16.1	0.4, 16.1	0.8, 29.1

1: White, 2: Relative risk, 3: Confidence Interval

Among White Ranch Hand veterans who spent 100% of their Southeast Asia tour of duty in Vietnam, the risk of prostate cancer was not significantly increased in any dioxin exposure category.



Melanoma Ranch Hand 100% Comparison 0%¹



	Comparison (N=580)	Ranch Hand		
		Bkg (N=287)	Low (N=151)	High (N=174)
N (%)	2 (0.7)	5 (2.0)	4 (3.0)	3 (1.8)
RR²		3.9	7.2	5.5
95% CI³		0.4, 35.3	0.9, 58.8	0.7, 46.1

1: White, 2: Relative risk, 3: Confidence Interval

Among White Ranch Hand veterans who spent 100% of their Southeast Asia tour of duty in Vietnam, the risk of melanoma was not significantly increased in any dioxin exposure category.



Conclusions



- **Not designed to directly assess the Vietnam experience**
- **Analyses**
 - **External contrasts with US White males**
 - **Internal dioxin categories restricted by time spent in Vietnam**

In a cohort study not designed to directly assess the Vietnam experience, we conducted external and internal analyses to assess the effect of time spent in Vietnam, tour date, and military occupation on cancer risk.



Conclusions



- **External analysis: Cancer at any SEER site not increased in either group**
- **External site-specific analyses**
 - **Increased melanoma in Ranch Hand veterans**
 - **Increased prostate cancer in both cohorts**

In external contrasts with national rates, the risk of all-site cancer was not significantly increased in either cohort. However, site-specific contrasts found a significantly increased risk of melanoma in Ranch Hand veterans and a significant increase in the risk of prostate cancer in both cohorts.



Conclusions



- **Internal analyses**
 - **At most 2 years in Southeast Asia**
 - **Cancer at any SEER site increased in High category**
 - **Melanoma increased in High category**
 - **Prostate cancer increased in High category**
 - **Ranch Hand 100% Comparison 0%**
 - **Cancer at any SEER site increased in High category**

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Internal contrasts by dioxin exposure category found a significant increase in the risk of all-site cancer, melanoma, and prostate cancer in the High dioxin exposure among those who spent at most 2 years in Southeast Asia. All-site cancer risk was significantly increased in the High dioxin exposure category in Ranch Hand veterans who spent 100% of their Southeast Asia tour of duty in Vietnam (referenced to Comparisons who spent 0% of their Southeast Asia tour in Vietnam).



Records collected and maintained include those of each participant, his children, and his spouse.



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Records have been scanned and are available to study staff through a Windows application.



Mortality End Points



- All causes
- External causes
- Cancer
- Cardiovascular disease
- Infectious-Parasitic
- Digestive diseases
- Liver diseases
- Endocrine diseases
- Ill-defined causes

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Periodic mortality assessments have been made since 1982. Information regarding underlying cause of death from death certificates is coded and classified into the categories shown.



All Cause Mortality to 31 December 1993



Stratum	Observed	Expected	RR ¹
Officer Pilots	39	40.0	1.0
Officer Administrators	2	2.5	0.8
Enlisted Flyer	21	28.4	0.7
Enlisted Ground	56	49.1	1.1
Total	118	120	1.0

1: Relative risk

Considering mortality after service in Southeast Asia to 31 December 1993, the risk of all-cause mortality was not significantly increased in Ranch Hand veterans. Stratification by occupation did not reveal any increased risk.



All Cause Mortality to 31 December 1999



Stratum	Ranch Hand	Comparison	RR ¹
Officer Pilots	56 (12.7)	677 (12.9)	1.0
Officer Administrators	7 (26.9)	47 (16.5)	2.2 ²
Enlisted Flyer	35 (16.8)	423 (15.0)	0.9
Enlisted Ground	88 (15.0)	1,183 (11.0)	1.3 ³
Total	186 (14.7)	2,330 (12.2)	1.2 ⁴

1: Relative risk, 2: p=0.05, 3: p=0.02, 4: p=0.06

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An update of the mortality data to 31 December 1999 revealed a borderline significant increase in the risk of all-cause Ranch Hand mortality and significant increases in Ranch Hand Administrative Officers and Ranch Hand Enlisted Ground Crew.



Cause Specific Mortality to 31 December 1993



Cause	Observed	Expected	SMR ¹
Accidents	26	22.3	1.2
Suicides	4	5.8	0.7
Homicides	2	1.7	1.2
Infection	2	1.3	1.5
Cancer	30	33.2	0.9
Endocrine	1	1.1	0.9
Heart disease	39	39.6	1.0
(Enlisted GC ²)	(24)	(16.1)	(1.5 ³)
Respiratory	2	4.1	0.5
Digestive	9	5.1	1.7 ³
Ill defined	3	2.4	1.3

1: Standardized Mortality Ratio, 2: Enlisted Ground Crew, 3: $p < 0.05$

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An analysis of cause-specific mortality up to 1993 revealed a significant increase in the risk of death from heart disease in Ranch Hand enlisted ground crew.



Cause Specific Mortality to 31 December 1999



Cause	Ranch Hand	Comparison	RR ¹
Accidents	30 (2.4)	360 (1.9)	1.2
Suicides	5 (0.4)	110 (0.6)	0.7
Homicides	3 (0.2)	27 (0.1)	1.8
Infection	2 (0.2)	28 (0.2)	1.1
Cancer	51 (4.0)	690 (3.6)	1.0
Endocrine	3 (0.2)	31 (0.2)	1.4
Heart disease	66 (5.2)	745 (3.9)	1.3
[Enlisted GC ²]	[40 (6.8)]	[393 (3.7)]	[1.7 ³]
Respiratory	8 (0.6)	96 (0.5)	1.2
Digestive	10 (0.8)	89 (0.5)	1.6
Ill defined	7 (0.6)	74 (0.4)	1.5

1: Relative Risk, 2: Enlisted Ground Crew, 3: p=0.001

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The corresponding analysis using information updated to 31 December 1999 showed an increased risk of death from heart disease in Ranch Hand enlisted ground crew, the subgroup with the highest dioxin levels.



Reproductive Outcomes

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Reproductive outcomes have been studied since 1982.



Reproductive Outcome Summary



Outcome	Findings
Hormones	±
Sperm count or abnormalities	-
Testicular abnormalities	-
Intrauterine growth retardation	-
Neonatal or infant death	-
Spontaneous abortion	-
Birth defects	-
Delays in development	-
Hyperkinetic syndrome	-

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We found no association between testosterone abnormalities and dioxin; mean testosterone decreased with dioxin, in the expected direction, however. We found no consistent or meaningful association between serum dioxin levels and follicle stimulating hormone, luteinizing hormone, testicular abnormalities, sperm count, or sperm abnormalities.

We studied paternal pre-term birth, intrauterine growth retardation (IUGR) and neonatal and infant death in children conceived during or after the father's service in Southeast Asia and based exposure on paternal dioxin measured in 1987 or 1992 extrapolated to the time of conception of the child. Children in the High (RR=1.3) and Background (RR=1.4) categories were at increased risk of pre-term birth. The risk of IUGR was not increased in any exposure category. The risk of infant death was increased in Ranch Hand children, with the greatest increases in the High (RR=4.5) and Background (RR=3.2) categories. We found no meaningful elevation in risk for spontaneous abortion or stillbirth.

In analyses of birth defects we found elevations in risk in some organ system categories, which were not found to be biologically meaningful. We found no indication of increased birth defect severity, or the risk of delayed development or hyper-kinetic syndrome with paternal dioxin. We found a trend of increased risk of spina bifida in Ranch Hand children with increased paternal dioxin body burden, but the counts were too small to analyze. The National Academy of Sciences concluded, in context with other studies, that existing data provided suggestive evidence of an association.



Summary



- **Cardiovascular mortality**
- **Hematologic findings**
- **Thyroid findings**
- **Diabetes**
- **Cognitive function**
- **Probable peripheral neuropathy**
- **Cancer**

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In summary, the study has found adverse associations between dioxin or herbicide exposure and cardiovascular mortality, some hematological measures, thyroid stimulating hormone, diabetes, cognitive function, probable peripheral neuropathy, and cancer.



Future Use Consent Summaries

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At the 2002 physical examination, participants were asked to consider giving their consent to the use of their data for future research after the programmed conclusion of the study in 2006. The choices to given to each subject were a) to allow the use of their data for Agent Orange or other military health research, b) for Agent Orange research only, c) no future use of their data for any purpose, d) other use. The results were tabulated and summarized here.



Overall Consent Summary



	Comparison	Ranch Hand	Total
Response	N (%)	N (%)	N (%)
AO or Health	1,138 (96.9)	731 (94.1)	1,869 (95.8)
AO only	23 (2.0)	32 (4.1)	55 (2.8)
Do not use	11 (0.9)	11 (1.4)	22 (1.1)
Other	2 (0.2)	3 (0.4)	5 (0.3)
Total	1,174	777	1,951

Most participants (95.8%) consented to Agent Orange (AO) or other military health research. The consent patterns were similar between groups.



Agent Orange Consent Definition



- **“Yes” if yes to**
 - Agent Orange or other military health issues, or
 - Agent Orange only
- **“No” if yes to**
 - Do not use, or
 - Other

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Responses were dichotomized to “Yes” if continued research (Agent Orange or other) was permitted, and “No” otherwise.



Agent Orange Consent Summary



	Comparison	Ranch Hand	Total
Agent Orange	N (%)	N (%)	
Yes	1,161 (98.9)	763 (98.2)	1,924 (98.6)
No	13 (1.1)	14 (1.8)	27 (1.4)
Total	1,174	777	1,951

Most participants (98.6%) consented to continued research and the patterns between groups were similar.



Ranch Hand Consent by Occupation



	Yes	No	
Occupation	N (%)	N	Total
Officer	305 (99.3)	2	307
Enlisted Flyer	132 (99.3)	1	133
Enlisted Ground	326 (96.7)	11	337
Total	763 (98.2)	14	777

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Among Ranch Hand veterans, the percentage consenting to future research was similar by occupation.

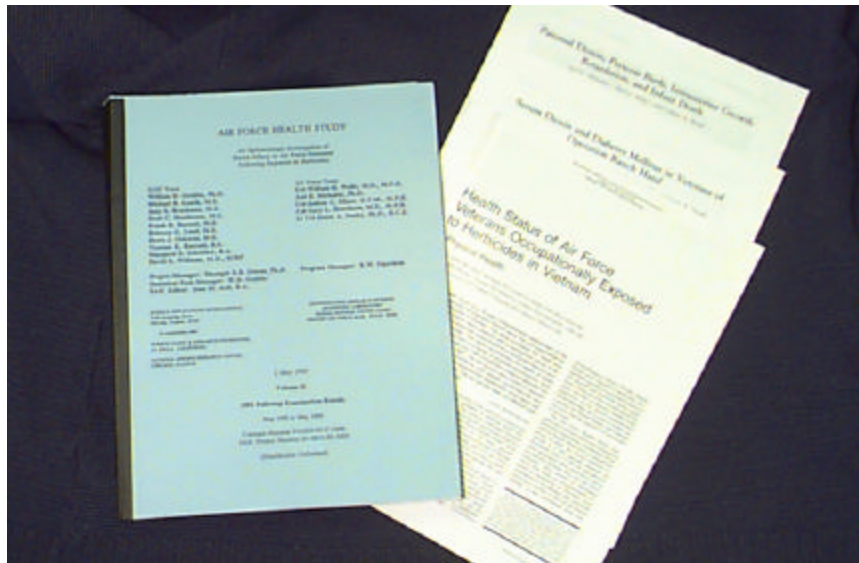


Comparison Consent by Occupation



	Yes	No	
Occupation	N (%)	N	Total
Officer	458 (99.1)	4	462
Enlisted Flyer	182 (98.4)	3	185
Enlisted Ground	521 (98.9)	6	337
Total	1,161 (98.9)	13	1,174

Among Comparison veterans, the percentage consenting to future research was similar by occupation.



The protocol, reports, and article citations are available on the study web page.



Web Page



www.brooks.af.mil/AFRL/HED/hedb/afhs.html

The study web page address is given. Questions and comments are welcome.